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IS THERE CARAMELIZATION IN RIVAS'S TEST?*

By David Wilbur Horn, Ph.D.

The object of this paper is to show that several phenomena accounted for by an *assumption* of caramelization may be accounted for by facts known to many chemists. The paper includes an experimental examination of one case where caramelization had been assumed by way of explanation.

In a paper read some years ago before the Pennsylvania Pharmaceutical Association, W. F. Horn called attention to the fact that when syrup of ferrous iodide has turned brown from age "we can readily restore its original color by boiling it in a flask for a few minutes."[1] J. P. Remington in discussing this point stated that one cannot "decolorize such syrup without the use of animal charcoal, because of the *caramelization*."[2] In a recent paper, West accounted for the appearance of yellow to brown colors on heating glucose broths with sodium hydroxide in Rivas's Test for *B. Coli* by stating that "The sugar is probably *caramelized* by the NaOH." "Lactose solution also becomes yellow to brown, depending on the amount of sugar."[3] More recently, in the discussion of the brownish color

* Presented at the meeting of the Phila. Section of the Amer. Chem. Soc., Jan. 20, 1910. Reread (by request) at the fifth Pharmaceutical Meeting for 1909–1910 at the Philadelphia College of Pharmacy, Feb. 15, 1910.

[1] Proceedings Penna. Pharm. Assoc., 1903, p. 112.

[2] *Ibid.*, p. 113.

[3] *Amer. Jour. Public Hygiene*, **19**, p. 228, 1909. Mr. West's statement was evidently not intended as more than a suggestion, for in a private communication, Feb. 15, 1910, he frankly states that he "has no sure ground to base his assertion on."

of a new, prepared milk, "Monia Milk," at a meeting of the Philadelphia Section of the American Chemical Society, *caramelization* was again resorted to as an explanation.[4]

Caramel is a dark brown substance formed when sugar is strongly heated. The action of heat on cane-sugar may be summarized as follows: When heated, cane-sugar melts at 160° C., approximately. Above its melting point, the sugar becomes colored, and finally changes into a brown mass called caramel.[5] The action of heat produces serious disturbances in the sugar molecule. This has been established since Lipmann observed, in the manufacture of candy, the formation of small quantities of dimethyl furfurol, pyrocatechinol, trioxybutyric acid, and trioxyglutaric acid.[6] Stone later proved that acetone is formed simultaneously with caramel.[7]

On glucose, the action of heat is as follows: The ordinary monohydrated glucose, $C_6H_{12}O_6 + H_2O$, loses its water gradually and without fusion at temperatures between 50° and 60° C. This dehydration is completed at 80° C. with partial fusion. Anhydrous glucose melts at 144° to 146° C. At 170° C. glucose is transformed into glucosan, $C_6H_{10}O_5$, with the loss of one molecule of water. At about 200° C. it darkens and forms a caramel similar to that obtained from cane-sugar.[8]

Caramel then is distinctly a product formed from sugars *at elevated temperatures.* If it is caramel that is formed at temperatures below the boiling point of water, for example when syrup of ferrous iodide ages at ordinary temperatures or when glucose or milk-sugar is warmed with alkalies as in Rivas's test for *B. Coli,* it would present a case of exceptional interest. I should regard it as hazardous to assert, without experimental proof, that because caramel is a brown decomposition-product of sugar, therefore every brown decomposition-product of sugar is caramel, and every process producing brown colors from sugar is a process of caramelization. By such argument, errors enter the literature of science masquerading as facts, and in direct opposition to the aim of science to eradicate the errors from the data accumulated.

The first experiments to test his assumption of caramelization,

[4] Meeting, Nov. 18, 1909.
[5] Les Sucres et Principaux dérivés, L. Maquenne, Paris, 1900, p. 656.
[6] *Ber. Chem. Gesell.,* Berlin, **26**, p. 3057.
[7] *Chem. News,* **70**, p. 117.
[8] L. Maquenne, *loc. cit.,* p. 486.

I made some years ago upon learning of the explanation of the browning of syrup of ferrous iodide. The results simply confirmed the statements of W. F. Horn. The color of the browned syrup vanished quite suddenly when the syrup was heated to boiling. Such evanescence is not a quality associated with the fairly permanent color, caramel.

When I met with the same assumption again recently in connection with Rivas's test, I undertook further experiments that I shall describe.

The first experiment [9] was intended to determine whether or not the formation of a brown color when the glucose broth is heated with sodium hydroxide is dependent on the presence of the peptone, or beef extract with the glucose at the time the alkali acts on it. Accordingly 5 c.c. 10 per cent. NaOH was heated with 0.25 c.c. portions of (*a*) a 1 per cent. glucose nutrient broth, (*b*) a similar nutrient broth to which the glucose had not yet been added, and (*c*) a 1 per cent. solution of glucose in distilled water. The color developed in both tubes containing glucose, but not in the tube of plain nutrient broth. Therefore the other constituents of the broth are not concerned with the formation of the yellow and brown colors.

In order to determine to how great an extent the glucose is involved in the action of the alkali, 45 c.c. of a 1 per cent. solution of glucose heated with 5 c.c. of water, and 45 c.c. of a 1 per cent. solution of glucose heated with 5 c.c. 10 per cent. NaOH, were examined successively in the polariscope. The effect of the alkali, it was found, was to destroy completely the optical activity of the glucose. Evidently, then, all of the glucose is affected by the alkali.

Upon adding sufficient acid to the browned solutions obtained by heating glucose with alkalies, the color immediately disappears.[10] This evanescence resembles that of the brown color in the syrup of ferrous iodide. Is the glucose restored to its original condition when the brown color is destroyed by acids? To answer this question, 49 c.c. of the browned solution described above was treated with 1 c.c. of water, and another 49 c.c. of the same browned solution was treated with 1 c.c. strong sulphuric acid, and the resulting solutions examined in the polariscope. Neither tube showed the

[9] The glucose used in these experiments was crystallized, C.P., monohydrated glucose.

[10] Cf. West, *loc. cit.*, p. 228.

slightest dextro-rotation. The conclusions are that the glucose is seriously involved in the action of the alkali, and that the brown color is the color of a secondary product.

To insure the dissimilarity of the brown color in the glucose solutions to the brown color of caramel, solutions of caramel made by heating glucose at 200° C. for 70 minutes and by adding "caramel brown" used for coloring whiskies to water, were used in the next experiment. Each solution was divided into two parts, one of which was acidified. The color of the acidified solution was then compared with that of the original solution corresponding to it. The acid produced a reduction in the intensity of the colors that was noticeable when a careful comparison was made, but the change was negligible when compared with the entire destruction by acids of the equally intense color of the browned glucose solution.

One of the well known tests for caramel was then selected and applied to the brown solution obtained when glucose is warmed with alkali. I selected Marsh's test as recommended by Crampton and Tolman [11] and used in their extensive researches on the aging of whiskies. The reagent is an emulsion made by adding 3 c.c. of water and 3 c.c. syrupy phosphoric acid to 100 c.c. amyl alcohol. When a whiskey colored with caramel is shaken with twice its volume of this reagent and time is allowed for two distinct layers to form in the liquid, it is found that the lower (aqueous) layer is always colored brown, whereas in the absence of caramel the lower layer is colorless. When, for the purpose of testing my preparation of this reagent, some of it was applied to a "straight whiskey" that I happened to have in my laboratory, the lower layer was colorless. When the browned glucose solution was tested in the same way, the lower layer was brown. Therefore, the test for caramel was positive. It is evident, however, that the results on the browned glucose solution are not comparable with those on the whiskey, for the glucose was alkaline and the whiskey, of course, acid. Accordingly the browned glucose solution was acidified and then tested as before, with the result that the lower layer was now colorless and the same solution that before gave a positive test now gave a negative test, for caramel. Similarly, some of the whiskey was rendered alkaline and then tested. The whiskey that had before given a negative test now gave a strong positive test, showing a brown color in the

[11] *Journ. Amer. Chem. Soc.*, **30**, p. 100, 1908.

lower aqueous layer. A fairly large amount of the original whiskey was now treated with the proper amount of Marsh's reagent, and the colorless aqueous layer drawn off by the aid of a separatory funnel. This lower layer immediately became brown when made alkaline, showing that the brown color was due to some substance extracted from the whiskey in the test. These results show the inadequacy of Marsh's test for caramel in alkaline liquids, and they also indicate the direction in which one may look for an explanation of the brown color formed when glucose is heated with alkalies. Before going further in this direction, however, some other experiments should be described.

I tried to obtain spectroscopic evidence of the similarity or dissimilarity of the browned glucose solutions and the solutions of the caramel made by heating glucose at 200° C., and the solution of "caramel brown." But none of them showed absorption bands in the visible spectrum, under the conditions of the experiment.

Oxygen gas (from an S. S. White cylinder of compressed oxygen) was then bubbled through the same three solutions. The color of the browned glucose solution began to fade very soon, whereas that of the other two solutions was unchanged. The gas was passed through the solution of the caramel made by heating glucose at 200° C. for 15 minutes without effect.

The last experiment performed was intended to test the validity of perhaps the strongest argument for the assumed formation of caramel when glucose solutions are heated with alkalies. These solutions are described in some works on urinalysis as smelling of caramel, especially after they have been acidified.[12] Now it is true that an odor of burnt sugar is frequently associated with caramel, but I failed to find this odor described as one of the properties of purified caramel.[13] Because I noticed that the solutions when hot and acid smelled more strongly than when cold, I subjected such a solution to distillation in a current of steam. The colorless distillate contained the odoriferous substance. I presume one must now abandon as misleading any argument based upon the so-called smell of caramel. It is evident from this one experiment that the

[12] Hammersten, *Physiological Chem.*, Mandel's Translation, N. Y., 1900, p. 80. See "Moore's Test."

[13] Sabanajeff and Antuschewitsch, *J. russ. Chem. Soc.*, 1893, p. 23; L. Maquenne, *loc. cit.*, p. 660.

odor and the color are not inseparably connected, and it is likely that the odor is due to another and colorless substance that may form at the same time caramel is formed, but may also form at other times as well.

The explanation suggested by some of these experiments is that in the browning of the glucose solutions we have to deal with the condensation of glucose molecules. Such condensation is to be expected because glucose is an aldehyde. In the pale yellow color that appears before the brown shades, and that may be preserved for some time by cooling the solution quickly, we may have to deal with an alcoholate or with mixtures of several alcoholates, formed by the action of the alkali on the alcohol groups of the glucose. The experiments with the polariscope suggest that racemization of the glucose molecule may also occur at the time the alkali acts.

Accordingly I examined the literature to see if I could find any ground against these suggestions or any evidence in favor of caramelization. I shall give data from several sources.

When a solution of glucose in absolute alcohol is treated with sodium ethylate, a compound is precipitated which when properly dried is a white to yellow-white powder of the composition $C_6H_{11}O_6Na$. When heated to a little over 70° C., this substance begins to brown and to decompose, even in an atmosphere of hydrogen, with the final formation of a brown, flaky, amorphous mass.[14]

"If an alcoholic caustic-alkali solution is added to an alcoholic solution of glucose, an amorphous precipitate of insoluble alkali compound is formed. On warming this compound it decomposes easily with the formation of a yellowish or brownish color, which is the basis of Moore's Test."[15]

When glucose is heated with water and potassium hydroxide in a loosely stoppered flask on a water-bath at temperatures from 35° to 40° C., the solution browns after a short time. This color increases in intensity for the first few days, but after some time the liquid becomes colorless. Lactic acid may be isolated from this colorless liquid with a yield of about 41 per cent. Although the rate of this reaction varies greatly with the dilution and the relative concentration of the alkali, lactic acid is always formed and may be separated from the colorless solutions that finally result. Sodium

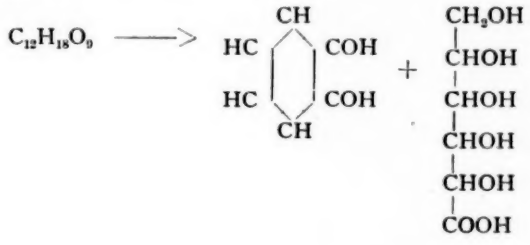
[14] Honig and Rosenfeld, *Ber. Chem. Gesell.*, Berlin, 10, p. 871, 1877.
[15] Hammersten-Mandel, p. 80.

hydroxide has exactly the same action as potassium hydroxide. Milk-sugar is also strongly browned by the alkalies, and decomposed with the formation of lactic acid.[16]

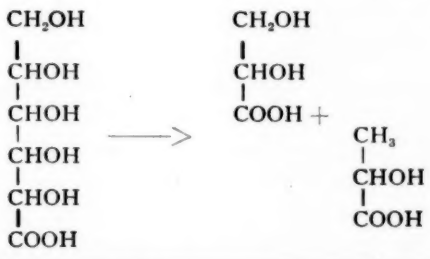
The exact mechanism of these changes has not been worked out, but Gaud [17] has thrown light on parts of the process. He was able to establish the formation of lactic acid, oxybenzoic acid, oxalic acid, and two isomeric dioxyphenylpropionic acids, also "melassique" acid and "glucique" acid constituting the greater part of the "resin" formed when copper oxide is also present with the alkali. These two complex acids had previously been described by Mulder in a paper entitled "Researches on Bodies of a Humus Nature." [18] According to Gaud, some of the glucose undergoes a dehydration and condensation under the action of the alkali with the formation of the complex "glucique" acid,

$$2C_6H_{12}O_6 = 3H_2O + C_{12}H_{18}O_9$$

This acid is unstable and breaks down into pyrocatechinol and gluconic acid:

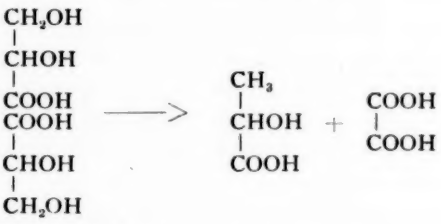


The gluconic acid separates into glyceric acid and lactic acid:

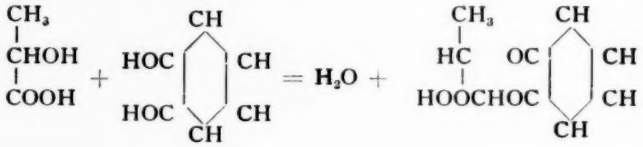


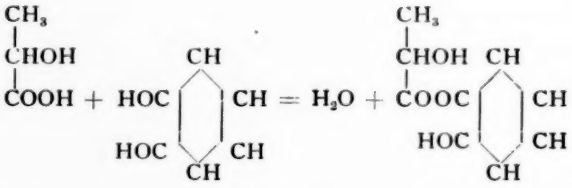
[16] Nencki and Sieber, *Journ. für prak. Chem.* (2), **24**, 498, 1881.
[17] Gaud, *Compt. rend.*, **119**, p. 604, 1894.
[18] Liebig's *Annalen*, **36**, p. 243, 1840.

In the presence of the alkali, the glyceric acid thus formed is transformed into lactic acid and oxalic acid:



Esterification then takes place between the lactic acid and the pyrocatechinol, formed earlier in the process, with the formation of two isomeric esters of hydrocaffeic acid, one of which has acid properties and the other alcoholic properties:





These citations serve to show the complexity of the changes when glucose is heated with alkali, and to suggest the desirability of further work. But they lend no color to the assumption of the formation of caramel, and they do not conflict with the explanation already suggested.

It seems likely that the yellow color developing at first when glucose is heated with an alkali, as in Rivas's Test, is due to some sodium glucose compound of the nature of an alcoholate. On further heating, the major part of the glucose is transformed into lactic acid and other of the organic acids mentioned by Gaud, and part of it is resinified as a result of its aldehyde group. Aldehydes as a class exhibit this latter behavior with alkalies. Thus, if acet-

aldehyde in aqueous solution is warmed with potassium hydroxide, the liquid becomes yellow and after a time reddish-brown amorphous masses are precipitated, " with the simultaneous production of a peculiar odor." The brown substance formed is called " aldehyde-resin."

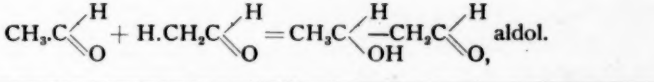
This method of explanation involves no new or improbable ideas. In fact, this behavior of aldehydes is given as characteristic of them, in the usual text-books of organic chemistry.[19] Further, this explanation is consistent with the facts in the case, even supplying some explanation for the bleaching action of molecular oxygen. For aldehyde-compounds would be expected to oxidize. It is also in accordance with the experience of every chemist who has added alkalies to alcohol, before distilling it to free it from aldehydes. The yellow to brown colors produced in alcohol under these conditions are also discharged by acids. And lastly, it explains the formation of a brown color in the almost colorless aqueous layer obtained in Marsh's Test applied to a straight whiskey, when this layer had been separated from the whiskey and then treated with alkali as described in the early part of this paper. For this aqueous layer contains aldehydes.

Milk-sugar gives similar results. An explanation may be found in this case, too, without recourse to the assumption of caramelization. Milk-sugar is well known to be readily hydrolyzed with the destruction of the monocarbonyl bond,

$$C_6H_{11}O_5{<}\,OC_6H_{11}O_5{<} + H_2O = C_6H_{12}O_6 + C_6H_{12}O_6,$$

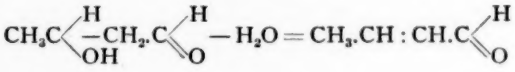
yielding d-glucose and d-galactose. It is also well known that alkalies, or rather hydroxyl ions, catalyze hydrolysis. It may well be, then, that in Rivas's Test the milk-sugar is first partly hydrolyzed into glucose which then reacts with the alkali as suggested above, with the production of the dark colored condensation products.

I do not wish to be understood as omitting the formation of aldols as a part of these condensations. Just as acetaldehyde forms aldol, so other aldehydes may be expected to:



[19] Holleman's *Organic Chemistry*, Tr. by Walker, N.Y., 1906, p. 135; Bernsthen's *Organic Chemistry*, p. 144.

This in no way invalidates the explanation by resinification. For it is probable that aldehyde-resin is a product resulting from the continued condensation of aldol molecules with the elimination of water, just as aldol itself easily loses one molecule of water when heated, with the formation of crotonaldehyde:



In closing, it seems permissible to return to the case of syrup of ferrous iodide. Although we deal here at first with a neutral syrup, it is possible to draw an explanation from the accepted facts of chemistry without recourse to the assumption of caramelization. Ferrous iodide is the salt of a weak base and a strong acid and therefore undergoes hydrolysis with the formation of hydriodic acid and ferrous hydroxide, or basic salts of ferrous iron, $FeI_2 + 2H_2O = 2HI + Fe(OH)_2$, or basic salts. The fact that this syrup becomes acid as it ages was pointed out by W. F. Horn in the paper already cited.[20] The cane-sugar then would be expected to undergo, at least in part, an *inversion*, or hydrolysis, such as it is well known to undergo in the presence of strong acids such as hydrochloric acid. As to strength, hydriodic acid is to be classed with hydrochloric acid, and it would catalyze this hydrolysis in much the same way as hydrochloric acid. This inversion would likely produce the two hexoses, d-glucose and d-fructose, well known to be produced in the presence of other strong acids:

$$C_{12}H_{22}O_{11} + H_2O = C_6H_{12}O_6 + C_6H_{12}O_6$$

These two hexoses may then undergo the change which is known as a general reaction for hexoses in the presence of hydrochloric acid, namely, the conversion into levulinic acid, $CH_3.CO.CH_2.CH_2.COOH$, with the simultaneous production of the brown substances known to be produced always in this transformation and called "Humus Substances."[21] Other reactions may occur at the same time,[22] and the browned syrup of ferrous iodide offers an open field for extensive investigation.

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[20] Proceedings Penna. Pharm. Assoc., 1903, p. 112.

[21] Holleman-Walker, p. 269.

[22] Cf. W. F. Horn, *loc. cit.*

In fact, the last word probably cannot be said in any of these cases except after elaborate research, but I believe there is ample evidence that the assumption of caramelization has no adequate experimental basis in the cases discussed, and that it does not even savor of probability, while the alcoholic and aldehydic characters of glucose may well account for the phenomena in so far as they are known at present.

PRIVATE LABORATORY, Bryn Mawr, Pa.
February, 1910.

A NOTE ON THE PREPARATION OF CHLORINATED SODA SOLUTION.

BY ELIAS ELVOVE.

The well known method of the U. S. Pharmacopœia (1905) for preparing chlorinated soda solution from chlorinated lime is certainly not a very simple method to say the least. We need only recall the fact that not only is it required to filter the aqueous mixture so as to free it from the insoluble portion remaining in suspension which is frequently a tedious and slow process, but that it is also required to afterwards remove the calcium from the solution by adding a solution of sodium carbonate and filtering off the resulting precipitate, thus involving a second tedious filtration. Again the fact that these precipitates are very bulky and difficult to wash thoroughly renders this process considerably wasteful as well as highly inconvenient when a comparatively large amount of this solution is to be prepared in the ordinary chemical or pharmaceutical laboratory. Also the fact that such preparations, even when kept under the most favorable conditions, are comparatively unstable and hence must frequently be prepared just when wanted, renders the disadvantages mentioned of even greater magnitude than would be the case if this preparation were of a stable character so as not to lose strength on long keeping. Finally, the fact that the chlorinated lime itself is a comparatively unstable substance renders it practically impossible to prepare a chlorinated soda solution of any desired strength, or even with any close degree of approximation, without having to carry out one or more actual determinations of the available chlorine in the resulting solutions.

Recently, a chlorinated soda solution containing about 6 per cent. available chlorine was required in the course of some experiments in the Division of Pathology and Bacteriology of the Hygienic Laboratory and the writer was requested to prepare such a solution. A trial of the present U.S.P. method, using of course proportionately larger quantities of the required substances, showed that this method is inadequate to yield a chlorinated soda solution of such high available chlorine content. The preparation of such a solution by direct passage of chlorine gas into a solution of sodium hydroxide suggested itself, and in looking up the chemical literature on the subject it was found that such a method has actually been employed by Graebe [1] and with very good results. Thus Graebe found that by employing a slight excess of the alkaline solution the stability of the resulting hypochlorite is much increased; for example, if instead of using just sufficient sodium hydroxide to combine with the chlorine, *i.e.*, in the theoretical proportion of Cl_2 to 2 NaOH, we use these constituents in the proportion of Cl_2 to 2¼ NaOH, he found that instead of a solution of over 5 per cent. available chlorine losing practically its entire available chlorine at the end of 3 days, it will still show the presence of 5.03 per cent. available chlorine even at the end of 6 days and although the temperature had risen from 18° C. to 25° C., if prepared so as to conform to the latter proportion; while by employing the chlorine and the sodium hydroxide in the proportion of Cl_2 to 3 NaOH, the resulting hypochlorite solution which immediately after preparation contained 5.7 per cent. available chlorine still showed the presence of 5.37 per cent. available chlorine even after having stood 23 days, during which time the temperature rose from 18° C. to 25° C. The effect of light, however, he found unfavorable to its stability and he therefore recommends that such solutions be kept in the dark. Graebe further points out the advantages of the method [2] for preparing chlorine that is based on the reaction between hydrochloric acid and potassium permanganate. Thus owing to the fact that this reaction is practically quantitative it is possible to prepare hypochlorite solutions of definite strengths by using the calculated amounts of the respective substances required. The chlorine thus obtained is also free from chlorine dioxide; and it is possible to carry out the whole process of generating the

[1] *Ber.*, **35**, 2753–2756 (1902).
[2] *Ber.*, **35**, 43–45 (1902).

chlorine and forming the hypochlorite solution without noticing the slightest odor of chlorine in the room in which the operation is carried out. About 65 c.c. of hydrochloric acid of sp. gr. 1.17 is required for each portion of 10 Gm. of potassium permanganate used, the evolution of chlorine commencing even without extraneous heating.

A chlorinated soda solution was therefore prepared by Graebe's method as follows: From the proportion

$$70.92 : 120 :: 6 : x = 10.15$$

we see that in order to have the proportion of Cl_2 to 3 NaOH, the amount of sodium hydroxide should be 10.15 per cent. in the case of a solution that is to contain 6 per cent. available chlorine. For making 500 Gm. of such a solution we will therefore need 50.75 Gm. of NaOH and 30 Gm. Cl_2 to 419.25 Gm. of water; while on the basis of 10 Gm. $KMnO_4$ equals 11 Gm. chlorine, to obtain 30 Gm. of the latter approximately 27.3 Gm. of the former will be required. These respective quantities of the several substances were therefore used in making this solution. The potassium permanganate was placed in a distilling flask of about 300 c.c. capacity, the mouth of which was fitted with a doubly perforated stopper; one of these perforations being used for connecting with the separatory funnel, into which 175 c.c. of strong hydrochloric acid (33 per cent.) was placed; while the other perforation in the stopper was used for uniting by means of suitable tubing the inner atmosphere of the flask with that of the separatory funnel; the latter being an arrangement used by Manchot and Herzog,[3] an illustration of which may also be seen in Loevenhart and Kastle's[4] paper on the catalytic decomposition of hydrogen peroxide. The delivery tube of the flask was connected with a small gas washing bottle (Drexel's), into which was placed about 50 c.c. of water for washing the gas before it passed into the sodium hydroxide solution. The latter was placed in a narrow-mouthed measuring cylinder, which it almost filled, and the gas delivery tube was made long enough to almost reach the bottom of the cylinder. When all the connections had been made, the stop-cock of the separatory funnel was turned so as to let the hydrochloric acid fall slowly in drops on the solid potassium permanganate in the flask. The

[3] *Ann. Chem.* (Liebig), 316, 321 (1901).
[4] *Amer. Chem. J.*, **29**, 397–437 (1903).

evolution of chlorine commences immediately after the acid and permanganate come in contact, and the rate of chlorine generated is easily regulated by the rate of flow of the hydrochloric acid. When the current of chlorine was observed to slow down, gentle heating was applied, and the operation continued until the current of chlorine passing the Drexel washing bottle was observed to have been reduced to just a very slow bubbling. The cylinder and contents were weighed before and after the passage of the current of chlorine and the increase in weight was found to be 29 Gm. This would make the added chlorine represent 5.81 per cent. of the final weight of the solution. An actual determination of the available chlorine in this solution, carried out by the U. S. P. method, showed the presence of 5.80 per cent. available chlorine. This shows therefore that the chlorine value of such a solution may be found by simply determining the increase in weight due to its passage into the solution; and it also shows that perhaps a better plan to follow when a solution of a given chlorine strength is required is to use a little more of the potassium permanganate than would correspond to the formula 10 Gm. $KMnO_4 = 11$ Gm. chlorine and determine the increase in the weight of the solution due to the passage of the chlorine into it; when, if the solution is found a little stronger than what is required, it could be diluted to the desired strength by the addition of the calculated amount of the sodium hydroxide solution. It would seem advisable therefore that Graebe's method for the preparation of chlorinated soda solution be adopted in the next revision of the U.S.P.; and perhaps also that the permanganate method for chlorine generation be used in all other pharmacopœial preparations where free chlorine is required, as, for example, in the preparation of chlorine water. This would not only avoid the use of different methods, as the chlorinated lime method for the preparation of chlorinated soda solution and the chlorate method for the preparation of chlorine water, but would also yield other advantages. Thus the latter would then be pure chlorine water instead of as at present containing also the foreign substances, potassium chloride and oxides of chlorine; while "the possible danger arising in the preparation of chlorine from either sodium or potassium chlorate and hydrochloric acid," pointed out by Merk[5] as being due to the decomposition with

[5] Proc. A. Ph. A., **52**, 775 (1904).

explosive violence of the oxides of chlorine which are generated in the chlorate process, would be avoided; also the difficulties pointed out by Shearer,[6] as the impossibility "even under the most favorable conditions, to obtain compound solution of chlorine containing 0.4 per cent. Cl as prepared by the U.S.P. formula," would be overcome; especially, when we remember that in passing the chlorine through distilled water preliminary to its entering the sodium hydroxide solution, we actually obtain in the one operation both chlorine water and chlorinated soda solution. Finally, the fact that the apparatus required is very simple and that it need not occupy much space, as well as the fact that the chlorine is readily generated by simply turning the stop-cock of the separatory funnel so as to allow the strong hydrochloric acid to come in contact with the potassium permanganate, and that the operation can be carried out so as not to notice the slightest odor of chlorine in the room in which this operation is carried out, would seem to offer the additional advantage of permitting the apparatus to be permanently set up and thus kept ready for use whenever free chlorine is wanted; while by also keeping ready for use a supply of the sodium hydroxide solution, the chlorinated soda solution could be prepared in a very short time and with very little attention.

It might be objected, however, that the permanganate method would increase the cost of the chlorine very much. But when we remember that a given weight of potassium permanganate can be used in making more than five times as much chlorinated soda solution as an equal weight of even the best commercially obtainable chlorinated lime, this objection loses much of the force which it might appear at first glance to have. Thus according to an experiment of Arny and Dawson,[7] in which 100 Gm. of chlorinated lime of an available chlorine strength which represented, according to these authors, about the best that is ordinarily obtainable commercially, was used in making 1000 Gm. of chlorinated soda solution by the U.S.P. method, the resulting solution contained only 1.65 per cent. available chlorine; or a total available chlorine of 16.5 Gm., the cost of the chlorinated lime for which would ordinarily be about 2 cents; while on the basis of 27.3 Gm. $KMnO_4$ + 175 c.c. hydrochloric acid yielding 29 Gm. available chlorine in the chlorinated

[6] Proc. A. Ph. A., **55**, 669 (1907).
[7] Proc. A. Ph. A., **56**, 842 (1908).

soda solution, and taking the average of the quoted wholesale prices for these substances, the cost of even 20 Gm. of such available chlorine need not exceed this amount, thus actually making the permanganate method even slightly cheaper than the present U.S.P. method, even if we do not consider its other advantages. It appears therefore that from whatever standpoint we may view the case the present U.S.P. method for the preparation of chlorinated soda solution is certainly not as advantageous as the method proposed as a substitute.

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A NOTE ON CERTAIN COLOR REQUIREMENTS OF THE U. S. PHARMACOPŒIA.

BY NORMAN ROBERTS, M.D.,
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Horace North, in Lehn and Fink's "Notes on New Remedies" for January, 1910, objects to the U.S.P. requirement as to the color of turpentine, in that there is no such thing as an absolutely colorless liquid, not even distilled water. This objection is valid, and to meet it definite color-limits should be officially set. The most practicable color standards would probably be dilute solutions of stable and easily obtainable substances, the comparisons being made in large colorless glass bottles or in Nessler tubes—not in test-tubes, since in a tube a flat bottom is necessary to avoid irregular dispersion and consequent inequality of the light.

Thus, in the case of Oleum Terebinthinæ, the first requirement should read somewhat as follows:

"A thin liquid, having a characteristic odor; color not more intense than that of a 1: (x) solution of (potassium dichromate) in distilled water, when viewed by diffused daylight transmitted from below, the bodies of liquid compared being one decimetre in depth and contained in similar Nessler cylinders 30 mm. or more in diameter."

Other liquids in the U. S. Pharmocopœia having the same vague

color requirement are as follows: Acetone, the various "colorless" liquid acids, ether, acetic ether, ethyl chloride, alcohol, water and a number of the medicated waters, benzaldehyde, benzin, bromoform, carbon disulphide, cinnamic aldehyde, eucalyptol, glycerin, guaiacol, a number of the liquors, methyl salicylate, oil of peppermint, oil of thyme, spirit of ammonia, spirit of nitroglycerin, terebene.

As no one color standard will do for all these liquids, a number of standards should be provided, and the liquid should be required to be *not more highly colored* than the designated standard, or if a given liquid is found at different times to assume two or more different colors in consequence of various impurities or deteriorations, a corresponding number of color comparisons may be prescribed. For certain of the "colorless" liquids, distilled water itself may serve as the color standard; for others, very dilute solutions of the decomposition products (*e.g.*, for hydriodic acid, iodine), but for most it will be necessary to experiment and find suitable non-related soluble substances by the use of which the usually occurring colors may be matched for practical purposes.

In many, perhaps most cases, a faint color may be present in officially "colorless" liquids, and still the liquid be for practical purposes as good as though it were water-colorless. The Pharmacopœia designedly permits such deviations from absolute perfection as will not result directly or indirectly in injury to the consumer, and will reduce what would otherwise be, in many cases, the prohibitive cost of production. But now that the U. S. Pharmacopœia is a pivotal legal reference work, vagueness of any sort must be eliminated, and all requirements stated in language which shall be, humanly speaking, unmistakable.

A NOTE ON CARDAMOM AND OIL OF CARDAMOM.

By George M. Beringer.

At the last annual meeting of the Pennsylvania Pharmaceutical Association the writer contributed formulas for some new basic elixirs that were proposed for introduction in the revision of the National Formulary. Among these was a compound elixir of cardamom in which the oil of cardamom is an essential ingredient. In the discussion following the reading of this paper, some doubt was

expressed as to authentic and pure oil of cardamom being available as an article of commerce and likewise as to its keeping.

These criticisms were not in accord with my own practical experience, as for nearly twenty years I had been using this oil continuously as a flavoring in certain special formulas and had found it very satisfactory, and during all this time I had experienced no difficulty in obtaining a good product nor had I any trouble in keeping it in my oil closet. The change noted in the latter respect was very slight indeed and not at all comparable with changes in such commonly used oils as lemon and orange.

The history of distilled oil of cardamom may be traced back to Valerius Cordus, who first distilled it somewhere about 1540. An oil prepared "by extraction from the seed" as suggested by the critic would be far from satisfactory, and his sample made as described, "by taking the cardamom seeds, grinding them and extracting with a solvent and evaporating the solvent," was probably not more than one-half to one-third pure essential oil, because the fixed oil in this seed is more abundant than the volatile and the ordinary solvents would extract this and leave it in the residue on evaporation.

The writer has always understood the commercial situation to be that a very large portion of the cardamoms harvested are not presentable and will not permit of bleaching either by natural or artificial means. Again part of the fruits become broken or dehisce from over-ripeness. Thus there is always available a relatively large amount of "decorticated" cardamom seeds freed from the almost inert pericarps and very suitable for grinding for manufacturing purposes and for distilling.

However, that there might be no question as to the abundance of a supply of pure oil of cardamom in commerce and that its keeping quality as well as purity might be established before receiving official recognition, further investigation was deemed advisable. The writer addressed a circular letter to a number of the large dealers and manufacturers of essential oils, propounding queries, answers to which would elicit the information desired. Their replies were uniformly prompt and courteous, and they willingly placed at the disposal of the committee data and information concerning the product. I acknowledge my obligation and appreciation of their kindness and am also indebted to Messrs. Dodge & Olcott Co., and the American Branch of Antoine Chiris for gratuitous samples. The object of

the present communication is to submit to the Committee on N.F. an abstract of the information thus obtained and the conclusions which I believe are warranted from these and my own observations.

"The official Malabar and Madras cardamoms are, on account of their high price, hardly ever used for the distillation of the commercial oil which is generally made from Ceylon cardamoms. Also this oil is rather high in price and would, therefore, never be used in larger quantities, so that the demand could probably be filled without difficulty. The keeping qualities of the oil are comparable to those of oil of lemon, orange, etc.

"The available data for testing the purity of the oil are somewhat meagre, and from what I suppose to be its chemical composition it would seem to be not very difficult to adulterate it without altering its various characteristics. Altogether, I would consider it as an article which does not lend itself well to official recognition."—Fritzsche Brothers.

"I am extremely friendly to the article—oil cardamom—knowing its value and worth as a flavoring ingredient.

"*Purity.*—This oil is one that is susceptible to adulteration, and an oil that has suffered tremendously in the past. We believe, however, that, along with other oils of this character, the standard has been raised considerably of late; and at the present time there is no difficulty in securing an oil as an article of commerce that can be officially recognized.

"*Distillation.*—There are several qualities of cardamom seed distilled, but the oils that are in most general use are drawn from the Ceylon and Malabar seed, both yielding a slightly different quality of oil; and in recognizing oil of cardamom, these conditions should be considered. We refer you to Parry and Gildemeister and Hoffmann, who have both analyzed these oils on a number of occasions, and our own laboratory has looked into same frequently.

"*Keeping Qualities.*—In our opinion, from the experience we have had with this article, the keeping qualities are much greater than that of the oil you mention. It is not prone to become terebinthinate and if kept under the ideal conditions that essential oils should be stored we believe it will retain its qualities for an indefinite period.

"*Physical Character.*—This is easily established and any prac-

tical chemist can differentiate between a pure product and an adulterated one; also between the several varieties.

"I would also add that the cultivation of cardamom seed has increased enormously of late, especially in Ceylon, and there will be no trouble in supplying any reasonable quantity that the trade demands."—P. C. Magnus.

"*Oil Cardamom.*—This oil has been sold more or less for medicinal and flavoring purposes, and while we do not know its consumption, we think that it is becoming an article of better demand and should be recognized officially, as it is prepared in sufficient quantities that it can always be obtained. We have not noticed any difference in the keeping quality of this oil and we do not see any reason of any change in the character of this oil or a good many other oils, provided they are absolutely pure.

"The following report of analysis of sample of oil of cardamom of our own distillation is submitted:

"Specific gravity at 15° C. ..... .9378
Specific gravity at 25° C. ..... .9320
Soluble in 4 vol. of 70 per cent. alcohol.
Optical rotation at 25° C. ..... + 29° 30′
Saponification number ..... 126.5"
—American Branch of Antoine Chiris.

"We have manufactured the article regularly for many years and in relatively a large way, the principal outlet for it being among manufacturers of high grade pharmaceutical preparations who presumably employ it as a flavoring agent in some of their compounded specialties. We do not class it among the especially sensitive oils and are quite certain that we have never had any spoil on our hands, notwithstanding the fact that under favorable conditions in respect of the raw material we sometimes manufacture ahead enough stock to last several years. Your first specific question as to whether the oil is prepared in sufficient quantity to be obtainable at all times we answer positively in the affirmative. We are always in position to supply the article of the very finest quality and in perfect condition.

"Your second question we have already answered substantially and we will add only that oil cardamom cannot be considered in

any sense as being in the same class with oils of lemon and orange in respect of keeping quality. The latter begin to deteriorate almost immediately on exposure, and unless light and air are carefully excluded from them they will become entirely spoiled and worthless in a comparatively short time. Of the cardamom, on the other hand, we have had an open bottle in use for a year or more without any noticeable sign of deterioration.

"Your third question we submitted to Dr. F. D. Dodge, chief chemist at our laboratory and factory, whose reply is as follows:

" 'I have no data as to the keeping quality of the oil, but from the fact that the terpene content is low, would assume that the product was relatively stable.

" 'As to tests: the oils manufactured here have generally agreed with the published descriptions of the Malabar oil. I have found as the result of 14 determinations (1907–1909)

" 'S.G. .933 — .943 at 15° C.
O.R. + 26° to + 40° at 15° C.

" 'According to some of the German investigators the oil should contain about 45 per cent. of ester, calculated as terpinyl acetate. I have not had occasion to determine this so far, but it could readily be done and, with the other constants, would be of assistance in valuing a sample. But I doubt if chemical tests alone would be sufficient to establish the purity or authenticity of the oil.' "—Dodge & Olcott Co.

"We have manufactured this oil for many years, and our product is used by some of the largest perfumers in France and America. We certainly think it is of sufficient importance to be officially recognized. It is an expensive oil, and therefore the actual weight distilled is not of course very great. We certainly think it is an oil that should be recognized, so as to keep out adulterated oil.

"We have found no trouble with its keeping properties, provided usual and reasonable care is taken not to expose the oil unduly to light and air.

"We think the physical characters and tests for purity can be readily established. In our own case, the raw material (cardamom fruit) we use for distillation is specially selected, not solely on the oil content, but with due regard to the odor value, which, as you

will readily understand, is a very important item in an oil which is used so largely in perfumery. It may interest you if we give you a few particulars of the tests of batches we have done during the last few years. Some of the tests were repeated more than twelve months after the oil was distilled, and the results did not vary appreciably:

TESTS FROM 1901 TO 1908.

Optical Rotation.	Specific Gravity.	
+ 30.5°	0.9474	
+ 12.25°	0.9102	Qualities not
+ 12.30°	0.9283	used by us.[1]
+ 36.88°	0.9315	
	0.9291	
	0.9330	
	0.9293	
	0.9322	
	0.9300	Sol. in 70% alc.
+ 31.6°	0.9349	1 in 4 vol.
+ 32.16°	0.9408	1 in 3 vol.
+ 30.6°	0.9309	
+ 29.75°	0.9302	
	0.9305	
+ 39.14°	0.9352	1 in 3 vol.
+ 28.00°	0.9322	1 in 3 vol.
+ 30.85°	0.9347	1 in 3 vol.
+ 31.2°	0.9357	1 in 4½ vol.
+ 30.75°	0.9349	1 in 4½ vol.
+ 28.25°	0.9365	1 in 3 vol.
+ 22.2°	0.9314	
+ 22.8°	0.9331	1 in 3 vol.
+ 24.35°	0.9329	1 in 3 vol.
+ 27.9°	0.9335	1 in 3 vol."

—Stafford Allen & Sons, Ltd.

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[1] "All our regular oil is distilled from Ceylon fruit.

"In 1901 we distilled a sample of wild cardamoms. These gave us an optical rotation of + 12.25 and a specific gravity of 0.9102.

"The same year we tried a sample of Mangalore cardamoms, which gave us a result of optical rotation + 12.30 and specific gravity 0.9283."

The latter firm print on their stationery as one of their important specialities "Cardamom Oil," indicating that it assumes a fairly important place in their commercial transactions.

I have recently examined three samples of this oil of different makes, the results being as follows:

	Specific Gravity.	Optical Rotation.	Solubility in 75% Alcohol.	Solubility in 70% Alcohol.
1.	0.9322	+ 32.6°	2 volumes	3 volumes
2.	0.9324	+ 29.4°	2 volumes	3 volumes
3.	0.9323	+ 29.4°	2 volumes	3 volumes

The data before us warrant the following conclusions: that ample supplies of pure oil are available; that it keeps as well as most essential oils and much better than many; that the commercial oil is largely distilled from cultivated Ceylon cardamom as well as from the Malabar; that the specific gravity varies from 0.929 to 0.947; that the oil is markedly dextrogyrous with quite a range running from + 22.2° to + 40°; that oils of lower specific gravity and optical rotation or deficient in flavor are obtained from wild or other cardamoms and must be rejected; that the pure oil is soluble when fresh in three volumes of 70 per cent. alcohol, and after aging somewhat is still soluble in 4 volumes.

The following is submitted as a proposed N.F. standard if the oil be admitted in the revision and follows the style of the U.S.P. VIII.:

OLEUM CARDAMOMI—OIL OF CARDAMOM.

A volatile oil distilled from the seeds of *Eletteria Cardamomum* White et Maton (Fam. Zingiberaceæ). It should be kept in well-stoppered amber-colored bottles, in a cool place, protected from light.

A colorless or very pale yellow liquid having the characteristic aromatic, penetrating, and somewhat camphoraceous odor of cardamom and a warm, persistently pungent, and strongly aromatic taste.

Specific gravity 0.924 to 0.947.

Very soluble in alcohol and dissolves readily and clearly in 4 volumes of 70 per cent. alcohol.

It is dextrogyrate, the angle of rotation varying from + 22° to + 40° in a 100 mm. tube, at a temperature of 25° C.

Cardamom and its volatile oil again illustrate the changes that

are continuously taking place in commerce and the need, therefore, of frequent revision of the statements in text-books and accepted authorities regarding the sources of drug products. Only a portion of the cardamom of commerce is now "obtained from the wild plants growing in the Malabar or west coast of India."

Since 1881, the cultivation of *Elettaria Cardamomum* in Ceylon has been very successfully carried on and the quantity of the fruit exported from there has been continually increasing, and the appearance and quality more and more closely simulating the best of the true Malabar product. "Ceylon-Malabar Cardamom" is now an established commercial variety [2] and the "Mysore" variety is likewise imitated and produced on that island. Hence the names heretofore used to designate commercial varieties of cardamoms now become meaningless as designating the countries of growth and export. Parry sums up this situation as follows:

"The majority of the cardamoms of commerce are imported from Ceylon and may be described as 'Ceylon Malabars or Ceylon Mysores,' according as they fit in with descriptions." [3]

Gildemeister and Hoffmann make the unqualified statement that, "The cardamom oil of commerce is not distilled from the official Malabar cardamom from *Elettaria Cardamomum* White et Maton, but from the long Ceylon, the wild growing cardamom of that island, the fruit of E. major of Smith, the *E. Cardamomum* var. β of Flückiger. They describe this oil as light yellow, somewhat viscid and having a specific gravity 0.895 to 0.905 and an optical rotation of $+ 12°$ to $+ 15°$ and yielding a turbid solution in 70 per cent. alcohol." [4]

They further state "that on account of their high price, the official Malabar and Madras cardamoms from *Elettaria Cardamomum* are seldom used in the manufacture of the volatile oil." They give the characters of the Malabar seed oil, specific gravity 0.933 to 0.943 and optical rotation $+ 26°$ to $+ 34° 52'$ and soluble in four and more parts of 70 per cent. alcohol.[5]

E. Parry [6] has examined samples of oils distilled from both

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[2] Arzneidrogen, Dr. Heinrich Zornig, Leipzig, 1909, fol. 196.

[3] Parry, Chemistry of Essential Oils and Artificial Perfumes, 1908, fol. 197.

[4] The Volatile Oils, Gildemeister & Hoffmann, translation of E. Kremers, 315.

[5] *Ibid.*, 316.

[6] *Loc. cit.*, 198.

Malabar and Mysore (Ceylon) seeds and reports that there was practically no difference, the result being:

	Sp. gr. at 15.5° C.	Optical Rotation at 16° C. (100 mm. tube).
Oil of Malabar cardamoms.....	0.9418	+ 40° 41′
Oil of Mysore cardamoms.....	0.9418	+ 46° 39′

The wild Ceylon cardamom is not an article of importance nor does it enter commerce in any large amount. In the communication above Messrs. Stafford Allen & Sons state that their experiment with distilling the oil from wild seed was unsatisfactory and they use only the cultivated Ceylon seed for their product, and this is also undoubtedly the practice of the other manufacturers. None of the oils examined showed results comparable with the data reported for wild Ceylon cardamom oil. On the other hand, the reports of Parry, Allen, Dodge, and Chiris as well as my own limited examinations all confirm the statement that the oil now on the market is distilled from the fruit of *Elettaria Cardamomum* and that the statement of Gildemeister and Hoffmann in this respect needs correction.

SOLUBILITY OF ALKALOIDS OF CINCHONA BARK AND THEIR SALTS IN WATER AT A TEMPERATURE OF 25° C.

By George L. Schaefer.

At the request of the editor of the Journal I submit a list of cinchona alkaloids and salts of which the solubility in water at a temperature of 25° C. has been determined.

I desire to call attention to the fact, that some of these salts are partly decomposed by water into a more soluble and a less soluble compound, which property, no doubt, has caused many of the discrepancies in previous determinations, carried out in different ways. For instance, 1 part of a pure basic salt of quinine glycerophosphate of the formula $(C_{20}H_{24}N_2O_2)_2PO_4H_2.C_3H_7O_2 + 5H_2O$ requires for complete solution about 850 parts of water of 25° C. If, however, a large excess of this salt is treated with water of 25° C. for several hours and frequently shaken, the solution filtered off from the undis-

solved part and tested, the salt will be found of a much greater solubility, requiring even less than 200 parts of water for solution, according to time and quantity used. The remaining undissolved part, when dried and treated again with water in the same proportion and under the same conditions as before, shows further decomposition, but in a lesser degree, and the solution will be found to contain considerably less of the salt than the first solution, and so on. Some others of the salts of cinchona alkaloids act more or less in the same way. Therefore the figures in the appended list show in each case that proportion of water which is required to make a solution with one part of the pure and finely powdered salt, when kept at 25° C. for several days, the mixture being frequently shaken. The results from tests obtained from saturated solutions made with a large excess of the salts or taking the difference between the quantity of the substance used and the weight of the undissolved and dried salt, in many instances, when testing salts of the cinchona group, show too great a solubility of the substances, the solutions containing a more soluble compound than the original salt, leaving undissolved a less soluble residue. The same salts also show a greater solubility when treated with hot water, the mixture allowed to cool off to 25° C., and kept at that temperature for hours to crystallize.

For the determination of the solubility of the pure alkaloids—quinine, cinchonidine, cinchonine and quinidine—I used saturated solutions, which were shaken out with chloroform or ether, as the nature of the alkaloid required, and determined by weight after evaporation of the solvent. The solubility of these alkaloids in water differs greatly, according to age and method of manufacturing. The figures in the appended list are obtained from products made a short time ago, but cannot be used as fixed standards. Other specimens of these alkaloids may be found to be more or less soluble, though chemically perfectly pure, the physical condition and amount of water of crystallization being responsible for the discrepancies. The same can be said of the tannates. Other salts of these alkaloids formed with volatile organic acids also become less soluble by age.

I trust that this paper will be of some use and regret very much not to have the time at present to give more complete figures, including the solubility of chinchona salts and alkaloids in alcohol, ether, etc., the published figures being in many cases incorrect.

The following table gives the amount of water required to dis-

solve one part of the alkaloids of cinchona bark and their salts at a temperature of 25° C.:

	Parts of water required to dissolve 1 pt. of the substance
Quinine alkaloid	3000
Quinine acetate	50
Quinine anisol	2400
Quinine arsenate	650
Quinine benzoate	360
Quinine bihydrobromide	5
Quinine bihydrochloride	0.7
Quinine bihydrochloride with urea	1
Quinine bisulphate	8.5
Quinine chlorhydrosulphate	1.3
Quinine chromate	3150
Quinine citrate	825
Quinine glycerophosphate, basic	850
Quinine hydrobromide	43
Quinine hydrochloride	21
Quinine hydroferrocyanide	2000
Quinine hydroiodide	205
Quinine hydrophosphite	35
Quinine lactate, basic	6
Quinine nitrate	70
Quinine oxalate	1400
Quinine phosphate	800
Quinine picrate	3400
Quinine quinate	3.5
Quinine salicylate	2100
Quinine sulphate	700
Quinine bi-sulpho-guaiacolate (guaiaquin)	0.5
Quinine sulpho-phenate	250
Quinine urate	550
Quinine phenol sulphate	680
Quinine tartrate	950
Quinine tannate	2000
Quinine valerate	80
Cinchonidine alkaloid	4800
Cinchonidine bisulphate	1
Cinchonidine tetrasulphate	3

Cinchonidine bihydrobromide	7
Cinchonidine hydrobromide	60
Cinchonidine hydrochloride	21
Cinchonidine bihydrochloride	1.6
Cinchonidine salicylate	1320
Cinchonidine sulphate	92
Cinchonidine tannate	1800
Cinchonine alkaloid	8800
Cinchonine bisulphate	1.5
Cinchonine hydrochloride	22
Cinchonine hydrobromide	59
Cinchonine bihydrobromide	1.8
Cinchonine salicylate (cryst.)	590
Cinchonine sulphate	85
Cinchonine tannate	1100
Cinchonine tartrate	32
Quinidine alkaloid	6900
Quinidine hydrobromide	190
Quinidine hydrochloride	86
Quinidine hydroiodide	1220
Quinidine salicylate	1650
Quinidine sulphate	95
Quinidine tannate	2100
Quinidine tartrate	35
Quinidine bitartrate	310

THE U.S.P. MELTING POINTS.*

By G. A. Menge, Ph.D.,
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Any one who has had occasion to apply, to any great extent, the various tests prescribed by the U.S.P. will, I believe, agree with me in the assertion that some of them are sorely in need of investigation and standardization. Perhaps to no class of tests does this statement apply more forcibly than to melting points. The chemist

* Read before the City of Washington Br. of the A. Ph. A., Mar. 2, 1910.

or pharmacist, although of excellent and broad training, who has not given the subject of melting points some special consideration and study might very reasonably ask, "What are the facts which call for and justify such an investigation?" In answer I would point to the discrepancies, sometimes very marked, that exist between the values published for the melting point of the same compound, as found in various sources of the chemical and pharmaceutical literature. In striking illustration of this fact I would submit data, collected from six different pharmacopœias and the important sources in the literature, upon the two compounds acetanilide and resorcinol: For acetanilide the six pharmacopœias agree within a range of 1° (113–114°), but four different sources in the literature give four different values ranging from 112–116°. In the case of resorcinol the values vary from 109–119°.

The wide variation in the published melting point values of these two compounds is certainly too great to conveniently hide behind the shield of legitimate "experimental error," yet they are only two of many, more or less similar, examples that might be cited.

In the case of acetanilide the fact that all of the pharmacopœias included in the comparison quote practically the same values for the melting point, also for the boiling point, is very striking but might be misleading. The remarkable concordance often found in the data of different pharmacopœias with reference to a given compound might suggest reliable values, but further study and comparison is apt to lead, first to the suspicion and then to the conviction that it more probably indicates the respect and confidence that the builders or compilers of one pharmacopœia feel toward those of another.

Another striking fact, in answer to the same question, is the protest of pharmaceutical chemists and manufacturers against the melting point standard required by the U.S.P., and the plea for the allowance of a varying margin of several degrees at moderately high temperature above and below that standard; all of which indicates a chaotic condition with regard to melting points that certainly calls for a thorough investigation. And in view of the fact that the U.S.P., through the operation of the Pure Food and Drugs Law, has become a legal standard, and because of the very general use of the melting point as one of its most important tests, it would seem of especial interest and importance to the Pharmacopœia and to all who are in any way connected with it that the

cause or causes of such conflicting values, or of reasonable protests, should be determined and, if possible, eliminated—if not completely, at least to as great a degree as is practicable.

The question naturally arises—"What are the causes of this divergence and what is the remedy?" I would summarize the main causes, though perhaps imperfectly and incompletely, as follows:

1. The great variety of methods used in melting point determinations.

2. Varied individual manipulation, including the so-called "personal factor," and especially the rate of heating.

3. Differences in the physical condition of the compounds.

4. The use of thermometers differing widely in their construction or range, or both.

5. The application or omission of emergent-stem correction and the manner of making it.

6. Widely varying interpretations of just what the melting point is (which might be considered to include the apparent use of decomposition point as equivalent to melting point).

The remedy may be indicated, to a greater or less degree, by a brief discussion under each of these different headings.

A description and detailed discussion of all the methods for melting point determinations that I have so far found described in the literature would doubtless be interesting and instructive but would, I fear, unduly tax not only your patience but also your endurance, and mine. Some of them—designed to eliminate certain specific difficulties in obtaining accurate results—are ingenious, more or less complicated, devices which impress me as being rather fantastic, and impossible of general application.

The methods prescribed by some of the pharmacopœias are, in the main, simple and practical but have not been sufficiently developed, it seems to me, to insure the degree of uniformity in results of which they may be capable.

That the use of different methods constitutes a real cause of divergence in results is, I believe, pretty generally recognized but may perhaps be more emphatically indicated here by citing some very good work in demonstration of this fact.

In 1889 Landolt published the results of a very careful investigation to test the comparative accuracy of several methods, including the determination of the melting points and of the freezing points of compounds with thermometers dipping into the substance;

also various modifications of methods involving the use of capillary tubes (including Piccard's)—using both liquid and air baths; and certain electrolytic methods. These were applied in determining the melting points of three substances (naphthalene, mannite, and anthracene), melting at about 80° C., 165° C., and 200° C. respectively. *The results obtained for each of these compounds under the same conditions by different methods were variable.*

In 1890 Reissert followed with the publication of somewhat similar work. He used only three methods, all of which were included in Landolt's investigation, but extended his experiments to a much larger number of compounds (24). Here again we find differences in the values obtained for the same compound by different methods—the divergence ranging from a few tenths of a degree at low temperatures to several degrees at high temperatures.

Perhaps the most comprehensive comparative study of different methods that can be found in the literature is that of Tyrer and Levy, published in the Year Book of Pharmacy, 1899 and 1900. In the course of their investigation nine different methods were used, including that described by the British Pharmacopœia, Graebe's, Landolt's, Piccard's, Loewe's, Mill's, Kuhara and Chikashige's, and Levy's acoustical method. Twelve compounds were treated, ranging in melting point from about 40° C. to about 200° C.

Besides the divergence due to the use of different methods they studied the effect upon the melting point due to varying physical conditions of the compound, to the extent that they determined the melting point of the commercial product, the same dried, and the same purified until there was no further rise in melting point.

The amount of divergence resulting from the use of different methods varied not only with rising temperature but also between different compounds melting at about the same temperature, and ranged from about 0.5° at low temperature to about 3° or 4° at high. With only three compounds, however, was the comparison extended to all nine methods. These compounds were spermaceti, melting at about 43°, betanaphthol, at about 122°, and picrotoxin, at about 200°. The range of divergence in this case extended from about 2° for the first two compounds to over 6° for picrotoxin. The increase in range of divergence with increase in the number of methods tested upon the same compound under the same conditions is very striking and convincing.

Undoubtedly then the use of different methods is a real and

serious cause of discordant results in melting point determinations. In so far as this cause accounts for divergence in U. S. pharmaceutical practice, the remedy is obviously the adoption by the U.S.P. Committee on Revision of a carefully defined official method.

In an attempt recently made in the Hygienic Laboratory to select or devise a method which could be recommended for such a purpose it was not considered feasible to experimentally test a great variety of methods, nor indeed was such a time consuming procedure necessary, for the specifications laid before us by the Committee on Revision, calling for the utmost simplicity, availability, and economy consistent with reasonable efficiency, made possible the elimination by inspection of practically all methods except one or two which we considered to offer promise. Comparative experimental tests were made upon two methods but the conclusion was soon reached that the simpler—applied with carefully defined procedure—would probably easily meet all practical requirements of pharmaceutical practice and, at the same time, very greatly improve the present standard. This method consists of one of the capillary-tube variety, more or less modified to meet specific conditions as they developed. It involves the use of a simple round-bottom straight glass tube of about 30 mm. internal diameter and about 100 mm. long, flaring slightly at the top like an ordinary test-tube. This tube or container is fitted with a stirring device, which any one can make in a few minutes from a piece of small sized, thick-walled capillary glass tubing of such length that a double bend above the top of the container brings the outer end of the stirrer within easy reaching distance of the hand for convenience in manipulation. When in use the container is filled with a suitable bath to a depth which will permit of such an immersion of the bulb of the thermometer that the upper end of the bulb will be 2 to 3 cm. below the surface of the bath and the lower end of the bulb about equally distant from the bottom of the container.

For melting points up to 150° C.—or even to 180° C.—pure concentrated sulphuric acid was considered the most suitable and satisfactory bath. When fresh it can be used at much higher temperature but then its very irritating fumes make it decidedly objectionable. After much experimentation no bath could be found suitable for work at temperatures much above 200° C. which was not more or less objectionable because of fuming. This difficulty, however, was found to be effectively overcome by a slight modification

of the apparatus, which consisted in fitting the container with a cork, perforated for the thermometer and for the stirrer and with two or three small vents at the edge to avoid excessive pressure. With this modification, a very pure grade of cotton-seed oil, freshly distilled paraffin, certain mineral oils, and a few other substances could be conveniently used up to 300° C. or over; but they soon become colored and have to be frequently renewed. A bath was finally adopted consisting of a mixture of pure concentrated sulphuric acid and potassium sulphate in definite proportions as recommended by Mulliken.[1] In my experience this bath, contrary to the claims made for it, fumes at high temperature almost as badly as the pure sulphuric acid. With the simple cork modification the fumes would char the cork and quickly spoil the bath, but by attaching a disk of thin asbestos to the bottom of the cork and including a glass tube in the perforation for the stirrer both the fuming and the charring were effectively overcome and the bath could be used as high as 350° C., or even to 370° C., with perfect convenience and safety. In all cases where the cork modification was applied the stirrer, in order to avoid inconvenience in attaching the capillary tube to the thermometer, was made in two parts, the first part extending through and about one-half inch above the cork; the second part being the remainder of the stirrer as first described. The two parts are easily joined, with ample security, by means of a small piece of small bore rubber tubing. The advantage of such an arrangement in connection with the cork hardly needs further discussion.

The dark color gradually acquired by the bath from contamination with organic compounds can be readily cleared from time to time by adding a pinch of potassium nitrate and in this way continuous use for a large number of determinations is possible. I have myself made considerably more than 100 determinations without renewing the bath.

This method has been applied to the suggested standardization of the melting points of about 37 of the more important pharmacopœial compounds, involving from 4 to 8 or more determinations on each of 5 to 8 samples of the individual compounds (with a few exceptions). In making these determinations the bath was heated

[1] S. P. Mulliken: "Identification of Pure Organic Compounds," vol. i, p. 219.

by direct application of a small Bunsen flame to the walls of the container, special care being taken in all cases to insure a definite uniform rise in temperature within a certain range of the melting point. Further details of manipulation will be briefly indicated in my discussion of the remaining causes of divergence.

The 37 compounds mentioned above are, with some exceptions, included only in that class of pharmacopœial compounds whose melting point determination by a capillary tube method offers no complication. I believe, however, that the application of this method to all other classes (such as fats, waxes, etc.) involves only modification in details and procedure and not any material change of apparatus. Furthermore, I can see no objection to applying it as a modification of Landolt's method in those cases where it would seem feasible and desirable to determine the melting point or freezing point of a compound by using a comparatively large amount, with the thermometer dipping directly into the substance.

As an official method doubtless some will criticize the one suggested as being too crude to insure the degree of accuracy and refinement that is desired in a standard value. But it seems to me that the principal object in the standardization of melting points —at least from the present view of the Pharmacopœia—is, not so much to adopt a method which will insure the *utmost* degree of accuracy and refinement attainable, however desirable that might be, as it is to adopt a method which shall be readily available to, and easily applied by, all concerned with the melting points of pharmacopœial compounds, and which shall be capable of reasonably concordant results as obtained by different manipulators, which after all is a very fair test of accuracy.

Though intending to be brief I have doubtless devoted more time to my discussion of methods than would perhaps seem desirable in the scope of a short paper involving other phases, but in any standardization the question of methods is the fundamental and probably the most important consideration—which fact may offer some justification for my slight elaboration upon this point. My indulgence, however, will necessitate a very brief discussion of the remaining causes if this paper is not to unreasonably encroach upon the other features of your programme.

That varying manipulation in melting point work may result in different values for the same compound has been experimentally demonstrated, and is further indicated by the recommendations of

the manufacturers' committee to the Committee on Revision of the U.S.P.

The so-called "personal factor" or "personal equation" (or other synonymous phrase) is doubtless a material and legitimate cause of divergence to some slight extent in any equally conscientious work; but it is also readily adapted to the service of a screen or shield covering careless, indifferent, and hurried manipulation. The amount of divergence honestly due to the "personal factor," I am strongly inclined to believe, would, in this instance, at least come well within the limits of a reasonably rigid standard, and for practical purposes may therefore be disregarded.

In so far as divergence is due to manipulation of the apparatus we believe it to be due largely, if not entirely, to differences in rate of heating and the variable application of stirring—entirely omitted in most cases; very irregular in others.

In describing the official method I would recommend, as a remedy for such defects, that the rate of heating for different stages of the determination be definitely prescribed and that constant stirring be required throughout the experiment.

Under differences in physical condition, as a cause of divergent values, there are three main considerations: (1) the size of the individual particles of the compound; (2) the moisture content; and (3) the presence of impurity.

Pawloff [2] has shown experimentally, working mainly with salol, that the more finely divided a solid is the lower is the melting point—the magnitude of difference depending in some measure upon the purity. He finds that a powder composed of particles less than 2 μ (in diameter) melts, in the case of salol, 7°, in the case of antipyrine, 5–7°, and in the case of phenacetin, 4°, lower than particles of 0.5–2 mm. diameter.

Considering the wide range in size of the particles of the same product, as found in the market under different labels, the experimental results of Pawloff make it obvious that in order to eliminate this cause of divergence it is necessary to officially prescribe that all substances shall be finely powdered before being subjected to the melting point test.

The work of Tyrer and Levy, previously referred to in this paper, offers conclusive evidence, if any were needed, of the marked

[2] *Zeit. Physikal. Chem.*, **65**, 1–35 (1908).

effect that the presence of moisture—also, of course, impurity—may produce upon the melting point of a compound. For example, in this connection, their results with acetanilide, phenacetin, and antipyrine show a variation in melting point of about 1° between the commercial and commercial-dried forms and a variation of from 0.6°, in the case of phenacetin, to nearly 3°, in the case of antipyrine, between the dried and the purified forms. The question of moisture as a cause of variation in the melting points of pharmaceutical compounds would seem to be easily disposed of by requiring a definite period of adequate desiccation for the finely powdered substances before the melting point determination is made.

The question of impurity, however, it seems to me, is a much more difficult one. To attempt an exact standardization of melting points for a class of compounds in which a certain percentage of impurity is permissible opens a wide field of investigation, that so far as I can find, has barely been touched upon, and constitutes, at least in theory, a very complicated problem, the discussion of which is far beyond the scope of this paper. Any possible difficulty in dealing with this factor, however, does not, in my opinion, justify neglect and tolerance of other causes of divergence which can be readily eliminated.

Passing rapidly over the topics remaining for discussion:

The fact that the use of thermometers of different construction induces more or less variation in results suggests the desirability of adopting an official thermometer—or set of thermometers—as a part of the official method, and requiring that they be standardized. True, such a step introduces the objectionable element of expense, but surely not in a prohibitive degree, even for a very modestly equipped laboratory.

That the application or omission of emergent-stem correction is a real and serious cause of divergence is strikingly illustrated by the fact that if a thermometer of average construction—used in connection with the apparatus we have recommended—registers 200° as the melting point of a compound, the correction, in most cases, will amount to 3° or 4°. Obviously uniformity of practice in this respect should be required, and in the cause of accuracy the correction should be applied. The manner of making the correction may also cause variation and should therefore be clearly defined—or better still, if official thermometers were adopted, official corrections could be made, plotted in a curve on co-ordinate paper and published,

and from this official curve the correction, for any temperature, could be determined by inspection, thereby conducing to absolute uniformity in this particular.

Finally, what is the melting point? Some authorities say it is that temperature at which the substance first begins to melt; others, that temperature at which it is just completely melted; others, the mean of these values; and still others say that it is not a point at all (except in theory) but a *range,* with which I emphatically agree.

At any rate it should need no argument to convince that here is broad opportunity for wide divergence; nor to induce the conclusion that if standardization of this constant is to be effective a clear, unmistakable definition of the melting point is essential.

With regard to the decomposing point I am personally convinced that it should never be used as a test of purity, and this conviction is based upon experimental evidence with several compounds.

Anything like a complete treatment of the melting point problem, in its present application to the U.S.P., is impossible within the limits of a half-hour discussion. For the purpose of this meeting it seemed more desirable to briefly outline *all* the more important phases of the problem than to attempt a very detailed discussion of any *one* or *two.*

Note: The subject of this paper, and the work that has recently been done in the Hygienic Laboratory on U.S.P. melting points will be given more complete and detailed treatment in a Hygienic Laboratory Bulletin to be published in the near future.

CORRESPONDENCE ON THE RELATIVE VALUE OF MACERATION AND PERCOLATION.

In view of the statements contained in the Presidential address presented by Professor Oldberg to the members of the American Pharmaceutical Association at the Los Angeles meeting, on the subject of maceration, letters were sent to various persons, including both retail and manufacturing pharmacists, asking for their opinion on the relative merits of maceration and percolation. Abstracts of the replies received follow.—EDITOR.

Prof. H. V. Arny, Cleveland, writes: I beg to make the fol-

lowing suggestions which have come from my personal experience.

I. Too little attention is paid in the average percolation to *loss of menstruum,* both by evaporation and through absorption of the marc.

II. Loss by evaporation can be prevented by suitable apparatus similar to that used ordinarily in percolation of volatile liquids (see "Economic Percolation," Proc. A. Ph. A., 1892, p. 169).

III. To make percolation profitable, the alcohol in the moist marc should be recovered. As to the two methods, that of percolating the marc with water and collecting the percolate approximating the amount of menstruum with which the marc was wet has never appealed to me. Far better is distilling the marc with steam, nor is this process one which should frighten the retailer. In my own retail experience I used a steam distilling apparatus consisting of a *boiler* made from a one-gallon tin can, provided with a cork with two holes, through one of which passed a straight safety tube, through the other a bent tube to convey the steam, which passed into the *distilling jar* which consisted of a wide-mouthed half gallon candy jar. I kept a half dozen such candy jars on hand for this purpose and the moist marc from every percolation (even though only an ounce) was transferred to the jar, which of course was kept tightly corked. The jars were only half filled with marc and when the six jars were thus half filled, the distilling apparatus was rigged up and the alcohol from the 10–12 pounds of marc was easily condensed, the jar being removed from the current of steam when the distillate was no longer alcoholic and replaced by another one containing undistilled marc. Since teaching, I have found it difficult to secure corks suitable for the candy jars, and have had made at the local can factory 1-gallon tin cans with larger mouths than ordinary—as large as will fit the largest corks now obtainable. These are in some respects not as satisfactory as the jars which in our drug business were so abundant that the occasional breaking of one meant no real loss. Of course the steam distilling apparatus must include a *condenser,* a fact so self-evident that I mention it merely for the sake of completeness.

IV. There is a lack of appreciation of the very great importance of careful percolation. Given the same drug and the same menstruum despite careful warnings as to speed of percolation, twenty operators will obtain as "first percolates" fluids of almost

twenty different strengths. I am now compiling figures showing amount of extraction in fluidextract of gentian made by repercolation from the same drug and the discrepancy in results obtained so far is extremely disappointing to one who has always been a staunch advocate of repercolation. Perhaps, however, my later figures will prove more satisfactory, but at present I can only advise utmost care in packing of drug and speed of percolation, and further recommend to all making their fluidextracts by repercolation, to compare the amount of extract in, say, 10 c.c. of the finished product with the amount of extract obtained with same menstruum on completely exhausting 10 grammes of the same batch of drug.

C. F. Nixon, Ph.G., Leominster, Mass., writes: I am afraid that I am strongly biased in this matter, so much so that I can conceive of no argument in favor of maceration where percolation is possible. The objections to maceration as they occur to me are as follows:

1. The drug cannot be properly exhausted unless several fractional macerations are employed and this requires much time.

2. Drugs prepared for maceration cannot be so finely ground as for percolation, as it would be impossible to express the saturated liquid. For example, tincture of belladonna, No. 60 powder, could not possibly be made by maceration.

3. Maceration must be accompanied by expression, and the amount of pressure used has a direct influence on the finished product. It would be impossible, however, to direct the amount of pressure used for each drug, and the results could not be uniform.

4. Unless much pressure is used there is a greater loss of menstruum.

5. It appears to me an uncleanly and unscientific process.

6. The product must be filtered. In many instances this would be a slow and difficult proceeding, as fine particles pass through in the process of expression that would clog the filter.

I believe that the adoption of maceration would be a long step backward.

May I add that the last official process for making tincture of arnica is most unsatisfactory, so much so that I think it is seldom employed. It seems to me that arnica is the very last drug that should be manipulated by maceration.

Prof. E. A. Ruddiman, Nashville, Tenn., writes as follows: My experience on "The Relative Value of Percolation and Maceration" has been limited, so far as comparing these two processes on individual drugs is concerned. I have found the pharmacopœial directions, as when to percolate and when to macerate, generally satisfactory. I cannot agree with Professor Oldberg in the statement made at the Los Angeles meeting of the American Pharmaceutical Association "that any plant tincture of 10 per cent. strength can be far more conveniently prepared by maceration than by percolation, and just as effectively." That has not been my experience either in the manufacturing laboratory or in the college laboratory.

Two preparations made by percolation that have given me trouble are fluidextract of squill and tincture of opium. In the case of the former I have had frequently to resort to maceration and straining, and clearing by standing. In the case of laudanum I am fully convinced from experiments which I have made in preparing this tincture and assaying the product, and in assaying the tinctures made by a large number of druggists, that the official process does not exhaust the drug. The opium should be exhausted as directed under the tincture of deodorized opium and the percolate evaporated if necessary.

In some cases I have found it desirable to use a coarser powder for percolation than directed by the Pharmacopœia.

E. L. Patch, Stoneham, Mass., says: While maceration may be advisable for gum-resinous drugs, or drugs largely soluble, as guaiac, myrrh, aloes, etc., for the larger number of ordinary drugs percolation is to be preferred.

If maceration is resorted to in such cases (ordinary drugs) and stirring of the drug and menstruum is followed, quite a portion of soluble matter is retained by the drug and can only be removed by strong pressure, which is usually inconvenient and annoying. If, on the other hand, the vessel has an outlet permitting the saturated or supersaturated liquid to flow off at intervals, as in percolation, more thorough extraction should result. We should remember that percolation is a process of solution and subject to the same rules as ordinary solution, and is affected by extent of surface exposed to action of solvent, to character of solvent, temperature, etc. The solvent may extract certain principles from the upper layers of drug in a percolator and become a compound

solvent, exerting a greater range of solvent action on subsequent portions. It is not necessary for percolation to be continuous. After two or three days' maceration, percolation can proceed until the percolate shows evidence of less saturation and then be stopped for another short period of maceration. We have noticed that a percolation conducted at a temperature of 50° compared with the same drug and menstruum at 70° requires more maceration and much slower percolation to obtain the same degree of extraction. While the fact is well known, the principle is often lost sight of. We recall being shown over the laboratory of a retail pharmacy where the percolations were being conducted near a large window in the coldest portion of the room because so much less time was required of the workers at the inconveniently low temperature than was required at other processes. At the time of our visit the temperature was about 45° F. and the operator was not properly extracting his drugs. For general use the instructions of the Pharmacopœia, as to method of conducting percolation, are sufficiently explicit.

Wilbur L. Scoville, Detroit, comments as follows on this subject: I have never done any direct work on the comparative results of preparations made by maceration with those made by percolation. I am aware that the maceration process produces a tincture that is less prone to precipitate but under the best of conditions it is more wasteful, and the precipitation in the percolation process can be reduced to a minimum by mixing all the menstruum necessary before beginning, and so avoiding slight changes in the menstruum during the process. Furthermore, except in the cases of a very few oleoresinous, resinous, and astringent drugs, the active principles of which are easily accessible and quickly soluble, maceration is the more important part of percolation. Pressure percolators have been proved inadequate many times, and long macerations, seven to ten days, are frequently an advantage, particularly in making concentrated preparations.

While a trained worker, taking special pains in a series of comparative experiments, may show some superior results for the maceration process, I believe that the average worker, on whom the necessity for full maceration and slow percolation has been impressed, will get more uniform, and on the average better, results by the process of percolation. This is, however, a tribute to maceration quite as much as to percolation.

Prof. Philip Asher, New Orleans, contributes the following: An experience of twenty-two years in pharmaceutical laboratories with both methods is decidedly in favor of percolation.

In the case of the exudates, as asafetida, myrrh, etc., it has proven more satisfactory than maceration and obviates the unnecessary cleansing of the utensils, so common with the latter process.

The following has been the *modus operandi* employed: The receptacle is graduated. The neck of the percolator is plugged with cotton moistened with alcohol. Over this a layer of well-packed excelsior is placed, acting as a porous diaphragm. The asafetida is placed in the percolator and some alcohol added, but not sufficient to cover the asafetida. This is allowed to macerate a short time, after which the asafetida is disintegrated by *poking* it with a sharp stick. After standing a short while to allow settling, percolation is started, and the disintegration repeated if necessary. Instead of adding the required menstruum at once, it is preferable to add only sufficient to leave a small layer above the drug.

The above process followed as outlined exhausts the asafetida completely, long before all the menstruum has been used, as evidenced by lack of precipitation when a few drops of the percolate are permitted to fall into water.

By this method, the so-called fluid asafetida, as offered by the pharmaceutical houses, can be made, heat being absolutely unnecessary in any of the stages, which represents 50 per cent. of the soluble principles.

Dr. J. M. Francis, Detroit, discusses the subject as follows: Without entering into any prolonged discussion of the matter, we beg to say that our experience would seem to indicate that maceration in the original sense is not at all necessary and is not nearly so satisfactory, all things considered, as percolation when properly conducted. Consequently we believe we are correct in saying that the old form of maceration is hardly ever employed in our laboratory at the present time.

It might be well for the sake of clearness to state that by "maceration" we refer to the old procedure whereby an excess amount of liquid is placed in contact with the drug and allowed to stand or macerate for several days, the liquid then being decanted or drawn off; a fresh portion of liquid in excess being added to the drug, maceration continued, and the process repeated.

Of course the ordinary process of percolation always involves a certain amount of maceration. The Pharmacopœia directs that a drug shall be moistened, allowed to swell through the absorption of the liquid, then be transferred and properly packed in a percolator, be covered with menstruum and allowed to macerate or "soak" for a certain length of time; and the percolation is then carried out in the usual way. Such maceration as this, where only a relatively small amount of liquid is employed, is very necessary. Even where the menstruum is allowed to slowly flow upon the drug in process of percolation, maceration is taking place unless the passage of the liquid through the drug is carried on with undue rapidity. Maceration, however, involving the use of an excess of liquid and long standing, we consider wholly unnecessary and we do not find it desirable even in the manufacture of tinctures.

The above statement is the outgrowth of long and continued experience. You may perhaps remember that in the beginning all of our fluids were prepared by this process of maceration. The drugs were allowed to stand in contact with the liquid for days, sometimes for weeks, the liquid was drained off, and the marc was then placed in a hydraulic press and the remaining portion of the liquid contents were pressed out. This old process, while yielding very good results, was found to be very expensive in time through the loss of menstruum, and moreover yielded fluids which showed a marked tendency to precipitation on standing.

Prof. Leo Eliel, South Bend, writes: There has been so much said and written on the relative value of percolation and maceration in pharmaceutical operations, that it would seem as though the last word had been said. This subject has been under discussion for fifty years to my knowledge. But the fact that you are taking up this subject for discussion at your pharmaceutical meeting would seem to show that there is still something to differ on.

As you are asking for my personal experience, I would say that it is decidedly in favor of the process by percolation; my reason for this being that by this process it is possible to have a definite quantity of the soluble drug constituents in a definite quantity of fluid. This is not the case in maceration, as there will always be an indefinite amount of soluble constituents left in the marc. However, I might say that the official directions, in many cases at least, do not allow a sufficient length of time for maceration before percolation. My practice is to macerate for a period of from three

to five days before packing and percolating. Of course with such drugs as zingiberis this would not be required, neither would this apply to mucilaginous drugs, where it might release substances that retard percolation.

H. A. B. Dunning, Baltimore, presents the following view of the subject: In most processes used for the extraction of vegetable drugs by means of solvents, maceration forms a necessary part, but whether the complete extraction of the drug should be accomplished through continued maceration is a doubtful question.

While it must be admitted that the active constituents of vegetable drugs may be entirely extracted by maceration, there are, I believe, very decided objections to this method, in practice. The *modus operandi* in my opinion is cumbersome, requiring, frequently, the introduction of comparatively large quantities of powdered material into narrow necked bottles, which material subsequent to exhaustion with the menstruum must be removed. Besides the stock bottle, a stock container and also a maceration vessel is required.

It is a tedious method, requiring seven days and ofttimes more for completion, depending largely on the attention given it.

It is apt to be uncleanly because, due to the frequent agitation necessary, some of the liquid may be allowed to escape from the container and run over it; of course the use of a little water would obviate this objection. Besides, when mixtures are poured from one vessel to another spilling is likely to result, not mentioning loss.

The process is also likely to be inaccurate, depending greatly upon the personality of the operator, for if the mixture is not frequently agitated, extraction will be very imperfect in the time usually designated; particularly is this statement true in regard to drugs which have a tendency to form "gummy" masses when moistened. In this case the final resort is "poking" with a stick; sometimes the stick is poked on through the bottle or other container. Further, I am told by some of the older pharmacists, who have had a more extensive experience with this process than I, that it is all too frequently the practice of some persons to use a portion of the macerating preparation before the time allowance is complied with and that in many instances no adjustment is subsequently made.

The maceration processes of the German, French, and English Pharmacopœias direct that the required amount of drug be macer-

ated with a definite volume—weight in case of German and French Pharmacopœias—of menstruum, the mixture strained, and marc expressed, the liquids then mixed and filtered. There is no allowance made for increase in volume through the dissolved extractive matter. The finished preparations are therefore neither of known percentage or part solutions. The U. S. Pharmacopœial method avoids this, perhaps slight, inaccuracy.

There are a few points in the various pharmacopœias, regarding maceration and percolation which seem inconsistent to me, although, I grant, that there may be good reasons, which do not appear on the surface. I do not understand why the British authority directs compound tincture of cinchona to be prepared by percolation and compound tincture of gentian by maceration; nor do I comprehend why the British Pharmacopœia as well as the German authority directs fluidextracts, which represent a much larger proportion of drug than do the tinctures, to be prepared by percolation, while some of the British and all of the German tinctures are prepared by maceration.

There are several tinctures directed to be prepared by maceration by the U. S. Pharmacopœia, which, although I have heard reasons given for so doing, in accordance with my experience would be better prepared by percolation.

I find the process of maceration entirely unsatisfactory for the preparation of tincture of arnica, inasmuch as the drug acts much like a sponge, absorbing by far the greater portion of the menstruum with which it is macerated, and it is a very difficult proposition to express much of the adhering liquid, even by means of a "press." Besides the filtered tincture is not so clear and rich in color as that prepared by percolation. I might mention that I have frequently observed that in passing menstruum through a drug the latter while being extracted acts as a clarifying agent. In regard to the best method for the preparation of this tincture and other tinctures presenting similar difficulties, I recommend for consideration the English method of collecting a large portion of the required volume as a reserve percolate and then expressing the marc. I make this suggestion only in case a dreg still is not at hand or the fluid cannot be forced from the marc by water (I have rarely found this latter suggestion expedient).

I have recently had under observation a series of experiments with different processes for the preparation of compound tincture

of cardamom. The conclusions drawn from these experiments are as follows: The present U.S.P. method is entirely unsatisfactory. Besides having the shortcomings of all maceration processes the product was filtered with great difficulty; and the filtrate was by no means as bright and clear as that made by percolation. I did not observe much difference in the quantity of deposit, on standing. The addition of glycerin to the menstruum previous to extraction only serves to increase the proportion of inert extractive. It should, I believe, be added after percolation.

In the preparation of tincture of opium the drug could be extracted more readily if it were mixed with some inert non-adhesive material, like purified sawdust or powdered paper. In this connection it might be well to mention that, in my experience, it is difficult to completely exhaust opium by the prescribed amount of menstruum and I would suggest that it might be well to percolate the drug to exhaustion with a suitable menstruum after having set aside a reserve portion; the weak percolate being evaporated to a soft extract and dissolved in the reserve percolate, etc.

Tincture of aloes and compound tincture of lavender now prepared by maceration are both suitable for the process of percolation.

Referring to percolation, I may state without hesitation that this method of extracting drugs appeals to me very forcibly. It should be preceded, as is invariably directed by the leading authorities, by sufficient maceration to soften and disintegrate the cellular tissue, within which the extractive matter is enclosed. Indeed maceration to this extent is a part of the process of percolation. This process, in my opinion, avoids almost entirely the objections offered to the *modus operandi* of maceration. Even the temptation to abstract portions of the unfinished product is obviated because of the comparatively less length of time required for completion of the process when once in active operation. Yet it is true that the time of maceration, before percolation, may be cut.

The entire theory of percolation is convincing and I believe the theory is well borne out in practice. I know of no serious objection to this process unless, as I have sometimes heard stated, the final product after standing shows a greater proportion of inert sediment than does a like preparation made by maceration. This may be true, due to the action of solutions of extractive matter of different degrees of saturation upon different portions of the drug and the subsequent mixing of same. However, I have ob-

served no very great difference in this respect between the products of the two processes under consideration.

I hold very strongly the opinion that all drugs that are suitable to be extracted by maceration or percolation should be treated by the process of percolation, provided that the material is not of such character that the particles, when moistened with the proper menstruum, will adhere so closely that the menstruum does not properly permeate the mass, or when the characteristics are such that it would be harmful to the substance to reduce it to a state of division suitable for percolation. The degree of fineness should be sufficient to avoid permitting the menstruum to pass freely through the spaces between the particles of the drug. Finally, it is my belief, that those pharmacists who have become familiar with the process of percolation will endeavor to avoid maceration processes.

Irwin A. Becker, Ph.G., Michael Reese Hospital, Chicago, writes that the only U.S.P. process for tinctures which he has modified is that for tincture of capsicum, his process being as follows: The drug is macerated for from three to five days, followed by filtration, the marc being transferred to the filter as early in the process as practicable. Sufficient menstruum is added through the filter to give the required measure. The resulting tincture usually has a deeper color and appears more brilliant than that made by percolation. Tinctures were made from four different purchases of drug, three being those from local jobbers and the other being Gilpin, Langdon & Company's " powdered capsicum for percolation." One of the observations in this series of experiments was that while G. & L.'s powder was lighter in color than the others, the tincture is as deep colored as those made from the other powders.

Mr. Becker incidentally mentions that he has trouble in removing the last traces of petroleum benzin in the process for tincture of deodorized opium.

AMERICAN PHARMACEUTICAL ASSOCIATION.

SECTION ON PRACTICAL PHARMACY.

Our annual meeting will soon be here and the Committee on Practical Pharmacy and Dispensing, *the* section for the practical retail pharmacist, is soliciting papers.

Being a Pharmacopœial Convention year, constructive papers on U.S.P. subjects will be greatly appreciated and will also be helpful to the U.S.P. Revision Committee as well as to the members in general.

Select your subject as soon as possible, and in order to avoid duplication send in the title of your paper *now*.

Give this matter your immediate attention and let us make the Richmond meeting the most important, the most interesting, the most instructive, and the most enthusiastic in the history of the A. Ph. A.

OTTO RAUBENHEIMER,
Chairman.

PHILADELPHIA COLLEGE OF PHARMACY.

FEBRUARY PHARMACEUTICAL MEETING.

The stated pharmaceutical meeting of the Philadelphia College of Pharmacy was held Tuesday, February 15, at 3 o'clock, with E. M. Boring in the chair.

Dr. D. W. Horn read a paper entitled "Is there Caramelization in Rivas's Test?" (See p. 151.)

The paper was a suggestive one, and those taking part in its discussion were Dr. C. S. Brinton, Professors Remington and LaWall, and Messrs. R. W. Hilts, W. L. Cliffe, and the chairman. Professor Remington said there were some who claimed that the color of straight whisky stored for four years in charred barrels is due to caramel produced by the action of heat on the wood in the charring process, and asked in what respect the color of straight whisky differs from that of true caramel, at the same time stating that there are those who claim that the caramel-colored whisky is just as good as straight whisky. He then remarked that a reliable test would have to be found for whisky.

As instances of the darkening of sugary preparations, Mr. Boring cited that of commercial syrup of hydriodic acid when partly used,

and Professor LaWall that of Eastman's syrup, which contains strong phosphoric acid.

Dr. Brinton called attention to the fact that glucose is not a chemical compound, but is a mixture including dextrin and other foreign substances. He also spoke favorably of Marsh's test for caramel.

Prof. LaWall asked if Dr. Horn had performed any experiments to determine the specific action of different strong acids on sugar solution since he had assumed that in the syrup of ferrous iodide the sugar was hydrolyzed or " inverted " by the free hydriodic acid. Prof. LaWall also asked if Dr. Horn had tried to extract the " aldehyde resins " with immiscible solvents.

In answering the several speakers, Dr. Horn said: In his experiments he had used the well-defined chemical compound, the crystallized mono-hydrated d-glucose, and not the commercial syrupy mixture that Dr. Brinton evidently had in mind. Marsh's test, although it might well be satisfactory in testing *acid* liquids like whisky, was unreliable in testing *alkaline* liquids. With regard to a statement of Dr. Brinton's that alcohol after treatment with alkali may acquire a yellow color and yet not answer the test for aldehydes, Dr. Horn said that small quantities of aldehydes might readily be formed by the action of atmospheric oxygen on the $—CH_2OH$ group of the alcohol. Replying to Prof. LaWall, Dr. Horn said that he had not been interested in the specific action of different acids, and that this had no bearing upon his paper, for he had referred to the action of hydriodic acid at such dilutions that the action was to be ascribed to the hydrogen ion, and that at such dilutions all acids of the same class as to strength would yield hydrogen ions at approximately the same concentration. The anion produced no appreciable effect at these dilutions. He said that he had not tried the action of immiscible solvents, and that he was not convinced that the so-called " aldehyde resins " of the organic chemist were the same in character as the resins Prof. LaWall had in mind. Referring to the brown color of whisky mentioned by Professor Remington, Dr. Horn said that in the recent literature there was a paper showing that the brown sediments sometimes appearing in whiskies were aldehyde-compounds. Regarding the odorous principle that he separated from the brown solution, he stated that he had not yet had time to study it further, but that the solutions containing it sustained the life of some molds and that in so doing they lost their odor. In this connection, he

pointed out that caramel purified by dialysis is not described as having an odor.

Dr. Brinton called attention to an observation that in separating aldehydes from alcohol by treating with alkalies the color disappears even on standing, and that aldehydes do not appear to be present except in alcohol from colored barrels. Dr. Horn remarked that sufficient of the oxygen of the air would gain access under the conditions to produce aldehyde, and stated that sealing in glass was necessary to prevent the access of air.

Professor LaWall referred to the popular notion that the burning of sugar has a disinfecting action and to the claim that formaldehyde is one of the resulting products. Mr. R. W. Hilts stated that a French chemist had found that smoked meats and sausages will give the reaction for formaldehyde, and that in the burning of a number of carbonaceous (carbohydrate) substances, formaldehyde is produced.

George M. Beringer, Ph.M., presented some notes on the U. S. Pharmacopœia, stating that he desired to direct attention to one specific subject—namely, the relation of the practical pharmacist to the work of revision. He called attention to the minutes and reports of various committees on the U.S.P. of the Philadelphia College of Pharmacy going back to the earlier revisions, and in commenting on the amount and importance of their work said that he made the exhibit to show that retail pharmacists always took part in the work. The speaker contended that if retail pharmacists do not take up the various practical problems, then it is their fault if the Pharmacopœia is found better adapted to the needs of manufacturers and others. He said that every pharmaceutical society and every college of pharmacy should take part in the work with a view of making the Pharmacopœia the legal standard for those who follow it and who must stand by it.

Mr. Beringer said that no matter what physicians say in regard to admissions and deletions, the pharmacist must stand his own, the trouble with many physicians being that they are working on questions that especially interest them. As an illustration of this tendency he said that recently one of them had suggested the omission of krameria and its preparations, while according to his own experience they should be retained.

With regard to the dosage forms of medicines, he said it was clearly within the province of pharmacists to work out the formulæ for them, as for example in the case of phenolphthalein. As

examples of official preparations requiring an improvement in the formulæ and directions, compound tincture of gentian and fluid-extract of squill were mentioned. Continuing, Mr. Beringer said that Dr. Rusby's paper on "Crude and Powdered Drugs at the Port of New York during the Year 1907–08" (AM. JOUR. PH., **81**, p. 231; Proceedings A. Ph. A., 1908, p. 783) shows the extent to which certain foreign drugs are being imported and used in this country, and of these he mentioned mylabris (Chinese beetle), stating that according to his experiments this drug is not adapted for the liquid preparations owing to the excessive amount of fat present, but that it is suitable for the plaster, and that if admitted to the Pharmacopœia retail druggists should have the say as to which preparations it should enter. Saw palmetto was mentioned as an example of an official drug for which no formula was given, and the claim made that pharmacists should work out formulæ for preparations of it.

Professor Remington said with reference to Mr. Beringer's remarks that the physician could not be blamed for looking at these questions from his point of view, nor druggists from theirs, nor even chemists from theirs, one of them, B. L. Murray, having recently proposed the omission of iron and mercury from the Pharmacopœia. With regard to mylabris and many other imported drugs, he stated that the desire to make them official was based on the need of standards for them.

John K. Thum, Ph.G., presented some notes on the Pharmacopœia, and offered the following practical suggestions based in part on his own experience: (1) That benzoinated lard be prepared by dissolving 1 per cent. of benzoic acid in lard melted at a low heat; (2) that in view of the statements that the stronger the alcoholic menstruum the more stable the preparations of digitalis coupled with the opinion that deterioration of these preparations is due to a ferment, experiments should be carried out along the line of extraction with a stronger menstruum and in the making of quantities, as of the tincture, which would be used in a short time; (3) that antiseptic solution should not be retained in the Pharmacopœia and that the addition of glycerin would make it more palatable, while maceration with 0.40 Gm. of finely ground golden seal for 24 hours followed by filtration without the use of talcum would improve its appearance; (4) that the addition of 10 per cent. of glycerin to the formula for compound syrup of hypophosphites enhances both the appearance and keeping quality, and that an

increase of the sugar from 775 Gm. to 825 Gm. per liter causes neither precipitation nor fermentation; (5) that in the definition of ether the words "not less than 96 per cent., by weight of absolute ether or ethyl oxide" should be substituted for the words "about 96 per cent., etc.," and that the time limit of the test for aldehyde should be extended; (6) that the description of each crude drug should be followed by a list of all the official preparations into which it enters; (7) that whenever an official compound is made and sold by different manufacturers under different names, as hexamethylenamine, the Pharmacopœia should state that these apply to compounds similar to the official one; (8) that the ten official syrups now directed to be made by the use of fluidextracts should be made direct from the drug, for the reason that when made from fluidextracts from which the precipitates formed by aging have been removed, they do not represent the full medicinal value of the drug.

Dr. C. S. Brinton, chemist of the U. S. Food and Drug Inspection Laboratory, Philadelphia, read a paper on "The Pharmacopœia in Food and Drug Inspection Work," which may appear in a later number of this JOURNAL, and in connection with the presentation of which a number of interesting specimens were exhibited.

Referring to the subject of powdered asafetida, Mr. Boring said that physicians have very little idea of the physical character of the drug and that when it is ordered on a prescription he selects the tears, which are free from impurities, and powders them, and that furthermore the gum having the character of an emulsion, it is not difficult to effect its solution when ordered in this form.

Dr. Horn, in alluding to the subject of revision, said that there is one good book on organic chemistry—namely, Beilstein's Organic Chemistry; that it had been gotten out well once, and that it is being revised all the time, small volumes being added from time to time. Professor Kraemer called attention to the manner of revision of the Japanese Pharmacopœia, stating that while the new Pharmacopœia was being considered, certain subjects were published as addenda to the previous edition, thus permitting opportunity for criticism and revision.

On motion of Professor Kraemer a unanimous vote of thanks was tendered the speakers of the afternoon for their interesting and valuable papers.

FLORENCE YAPLE,
Secretary *pro tem.*